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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/270,006	03/16/1999	JEAN-PIERRE ROBIN	017753-113	1899

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EXAMINER

BALASUBRAMANIAN, VENKATARAMAN

ART UNIT	PAPER NUMBER
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1624

DATE MAILED: 12/30/2002

29

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/270,006

Applicant(s)

ROBIN ET AL.

Examiner

Venkataraman Balasubramanian

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 October 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 88-101 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 88-101 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 16 March 1999 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/17/2002 has been entered.

The declaration of Dr. Jean-Pierre Robin filed along with the above submission is also made of record.

Claims 88-101 are pending.

In view of applicants' response and submission, the following apply.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 88-101 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply. Any claim not specifically rejected is rejected as being dependent on a rejected claim.

1. Claim 88 is indefinite as it is not clear what proviso is to be applied when $n=0$.

Note there are two provisos when $n=0$ and the first one precludes R^5 to be

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CH_2COOH or CH_2COOMe but the second proviso permits such groups for R^5 . It is not clear what is intended.

2. Claim 93 is indefinite as it recites "n is included between 1 and 8". It is not clear what is intended. Is n to be greater than one and less than 8 in this case?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 88-94 and 100-101 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for $n=0,1,2,3$, does not reasonably provide enablement for $n=4,5,6,7,8$. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Following reasons apply.

In evaluating the enablement question, following factors are considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1. The nature of the invention and the state of the prior art:

The invention is drawn to compounds, which are one-oxygen containing heterocyclic compounds with ring size varying from 3 to 11. Specification is not adequately

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enabled as to how to make one-oxygen containing heterocyclic compounds with ring size varying from 7 to 11. In general medium and large ring compounds are difficult to make. Specification although teaches how to make 3 to 6-membered oxygen heterocyclic rings, specification offers no teachings or suggestion as to how to perform the process for making rings wherein $n = \text{more than } 3$. Furthermore, references cited in prior art do not teach compounds of the instant claims with larger ring size. In addition, it is clear from the declaration submitted by the applicants that the overall process of making cephalotaxine esters is difficult by conventional process and often leads to inseparable mixtures etc. Hence it is essential to have a viable process for making these compounds wherein $n > 3$.

2. The predictability or lack thereof in the art:

Hence the process as applied to the above-mentioned compounds claimed by the applicant is not an art-recognized process and hence there should be adequate enabling disclosure in the specification with working example(s).

4. The amount of direction or guidance present:

Examples illustrated in the experimental section or written description offer no guidance or teachings as to how perform the process of making compounds of ring size three to six but there is no guidance provided for ring size greater than six embraced in the instant claims.

5. The presence or absence of working examples:

Although examples shown in the specification provide guidance variously substituted 3 to 6 membered oxygen heterocyclic compounds, there are no

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examples shown that would suggest applicability of the process for higher ring size compounds. There are no representative examples showing the viability of the process for plurality of substituents with the variation in ring size embraced in the instant claims.

6. The breadth of the claims:

Specification has no support, as noted above, for all compounds generically embraced in the claim language would lead to desired compound of formula shown in the instant claims.

7. The quantity of experimentation needed:

The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired structure, namely compound of formula embraced in the instant claims in view of the prior art teachings.

Thus, factors such as "sufficient working examples", the "level of skill in the art and predictability, etc. have been demonstrated to be sufficiently lacking in the case for the instant claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 88-89 and 100 are rejected under 35 U.S.C. 102(b) as being anticipated by Wuts et al. Tetrahedron Letters 23: 3987-3990, 1982.

Wuts et al teaches several tetrahydropyran carboxylic acids and esters generically embraced by the instant claims. See page 3988 for compounds made.

Claims 88-89 and 100 are rejected under 35 U.S.C. 102(b) as being anticipated by Leroux et al. Bulletin De La Societe Chimique De France, 1; 344-351, 1968.

Leroux et al teaches several tetrahydropyran carboxylic acids and tetrahydrofuran carboxylic acids generically embraced by the instant claims. See entire document especially Table II and Table IV for compounds made.

Claims 88-89 and 100 are rejected under 35 U.S.C. 102(b) as being anticipated by Newman et al. Organic Reactions Volume V, 414-439, 1949.

Newman et al teaches several glycidic esters generically embraced by the instant claims. See entire document especially Table I for compounds made. Note the proviso in claim 88 does not exclude all compounds shown in the Table I.

Claims 88-89 and 100 are rejected under 35 U.S.C. 102(b) as being anticipated by Ciurdu et al. PL 103334, CA 121: 255399, 1994. CAPLUS abstract provided.

Ciurdu et al teaches glycidic esters generically embraced by the instant claims. See Answer 53 and compounds shown therein.

Claims 88-89 and 100 are rejected under 35 U.S.C. 102(b) as being anticipated by Reich et al. Biorg. Med. Chem. Lett. 4(9) 1167-70, 1994. CAPLUS abstract provided.

Reich et al teaches a glycidic ester generically embraced by the instant claims. See Answer 54 and compound with RN 34886-30-1 shown therein.

Claims 88-89 and 100 are rejected under 35 U.S.C. 102(b) as being anticipated by Kulesza et al. PL 85803, CA 90: 121390, 1979. CAPLUS abstract provided.

Kulesza et al teaches several glycidic esters generically embraced by the instant claims. See Answer 159 and compounds shown therein.

Claims 88-89 and 100 are rejected under 35 U.S.C. 102(b) as being anticipated by Genet et al. US 5,084,582.

Genet et al teaches glycidic esters generically embraced by the instant claims. See col. 2 for the process of making and examples 1-9 for compounds made shown on col. 3-5.

Claims 88-89 and 100 are rejected under 35 U.S.C. 102(b) as being anticipated by Chan et al. US 4,870,208.

Chan et al teaches glycidic esters generically embraced by the instant claims. See col. 1 and col. for compounds taught.

Claims 88-89 and 100 are rejected under 35 U.S.C. 102(b) as being anticipated by Bateson et al. WO 92/01696.

Bateson et al teaches tetrahydrofuran carboxylic acids generically embraced by the instant claims. See page 96-97 and 105 for compounds made.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 88-89, 95-96 and 100-101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. Yaoxue Xuebao (Acta. Pharm. Sinica) 27, 178-184, 1992(Wang I) and Huang et al, the Alkaloids, Vol. XXII 157-225, 1984 in view of Wang et al. Yaoxue Xuebao (Acta. Pharm. Sinica) 27, 173-177, 1992(Wang II) for reasons of record. To repeat:

Wang I teaches the tetrahydrofuran and tetrahydropyran esters of cephalotaxine. See compound 8 and 9. Note these compounds are known to exhibit antitumor activity.

Wang I differs in not making the tetrahydrofuran or pyran carboxylic acid first.

Huang et al. teaches the process for hydrolyzing the cephalotaxine alkaloids and the synthesis of the acid components. See page 165 for mild hydrolysis to get compound 7 and see route 3 on page 166. Wang II teaches a process for cyclizing the open chain acid ie compound 7 bearing a CTX group to the corresponding

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tetrahydrofuran compound. See page 174 of Wang II and note the last reaction shown at the bottom of the page using TsOH.

Note the starting materials are analogous in that they are compound of formula 7 with a methoxy on the tertiary carboxylic group or CTX. Thus one having ordinary skill in the art at the time of the invention was made would have been motivated to combine both the primary and secondary references and employ the process taught by these prior art to the starting materials and expect to obtain the desired product because he would have expected the analogous starting materials and reactants react similarly. It has been held that application of an old process to an analogous material to obtain a result consistent with the teachings of the art would have been obvious to one having ordinary skill. Note *In re Kerkhoven* 205 USPQ 1069.

Applicants' argument to overcome this rejection as noted in paper 28, is not persuasive.

Applicants have not shown why it would not be obvious for one trained in the art to take compound 8 and 9 of the primary reference and hydrolyze them to arrive at the tetrahydrofuran and tetrahydropyran carboxylic acid.

In addition, the declaration appears to be relevant for the overall synthesis not for making the intermediate compound by the process of hydrolysis taught by the secondary reference.

Hence this rejection is maintained.

Claims 88-89 and 100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsujihara et al. US 5,677,470.

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Tsujihara et al. teaches several epoxypropionic acids useful as intermediates to make baccatin derivatives, which includes compounds claimed herein. See compound of formula I on col. 3 and note the definition of X which includes instant R^6 and R^8 substituents. See col. 13-14 for process of making these epoxy compounds. See examples 1-31 for use of these compounds. Especially see tables 1-27 for compounds made.

Instant claims differ from the reference in reciting a phenyl group while reference teaches substituted phenyl groups.

However Tsujihara et al. teaches both the equivalency of herein exemplified substituted phenyl with those substituents claimed for X in col. 3. claimed herein. See cols. 2 and 3, formula I, especially the definition of X group. Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds variously substituted epoxypropionic acid as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (703) 305-1674. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is Mukund Shah whose telephone number is (703) 308-4716.

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The fax phone number for the organization where this application or proceeding is assigned (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

V. Balasubramanian
Venkataraman Balasubramanian

12/26/2002